Developing a route towards palustrine synthesis

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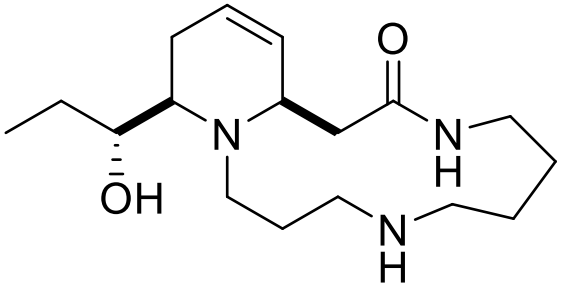
Project thesis, autumn of 2015



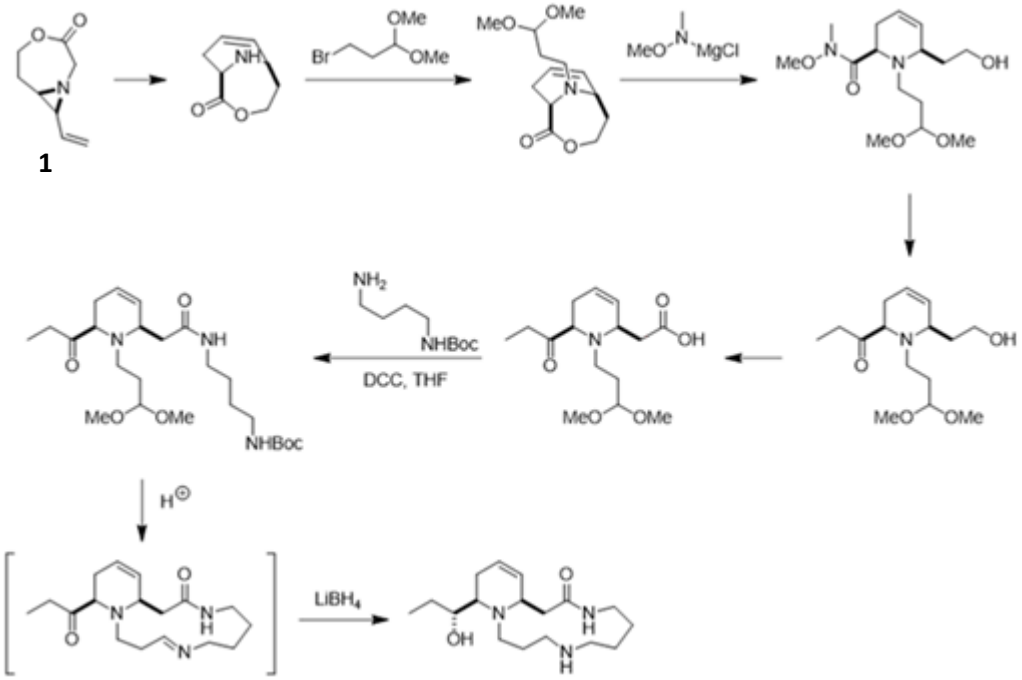
Abstract

Palustrine, a piperidine alkaloid, was retrosynthetically analyzed and two branches of a route to a key intermediate aziridine **1** tried – namely, nitrene formation through UV irradiation and 1,3-dipolar cycloaddition. Neither approach gave any positive results. After this the synthesis of a model compound was attempted, but ran into unexpected problems with performing radical terminal bromination of sorbates. The project overall achieved no notable positive results.

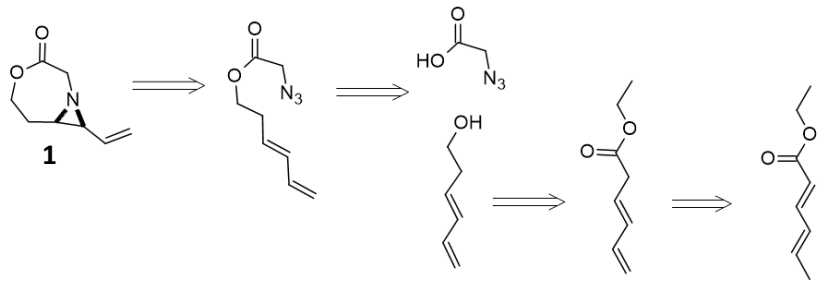
Introduction

Palustrine is a piperidine alkaloid found in the *equisetum palustre* plant species that grows in North America and Eurasia. It is often consumed by livestock through the plants, and is harmful as such, because of its LD_{50} of only 50 mg/kg, and its content in the plants of about 500 mg/kg of dry plant weight [1]. It was first isolated in 1948 [2] and its structure was confirmed by its first total synthesis in 1984 [3].

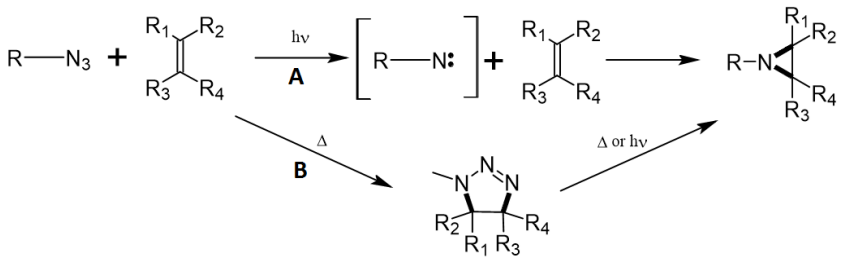
To develop a new route towards the synthesis of palustrine, a retrosynthetic analysis was performed:



The scope of this project was the attempt to achieve the key intermediate **1**. To this end, a further retrosynthetic analysis was done:



The key step here is the last step, aziridine synthesis. Aziridines from double bonds and azides can be achieved in one of two ways:



Through route **A**, the azide is excited by UV light and ejects N_2, forming a radical nitrene intermediate, which adds directly to the double bond, forming the aziridine [4,5,6,7,8].

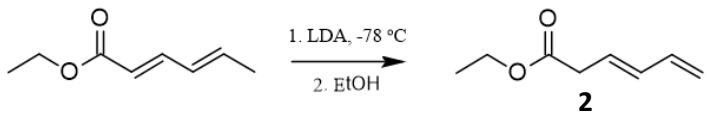
By route **B**, with the use of heating the azide and double bond undergo a 1,3-dipolar cycloaddition to form a stable triazoline intermediate. This intermediate can then be transformed into the aziridine either thermally or photochemically, resulting in loss of N_2 in both cases [9,10,11,12,13]. As aziridines are mostly quite thermally unstable, a photochemical reaction is often preferred in transforming the triazoline.

It is important to note that 1,3-dipolar cycloadditions are favored both in the case of an electron rich olefin and electron poor azide, and vice versa, but disfavored in the case of an inactivated azide and/or olefin [14]. In our case, both moieties are relatively inactivated and thus achieving a reaction between them may be difficult.

Results and discussion

Isomerization

To begin the synthesis, ethyl sorbate was isomerized by deprotonation and subsequent reprotonation at -78 °C to give the kinetic product **2** [15].



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Due to the extremely water- and temperature sensitive nature of the reaction, several tries were needed before sufficient mastery of the procedure was achieved to successfully acquire the product. Final yields were 70% at 1 gram scale and 53% at 5 gram scale.

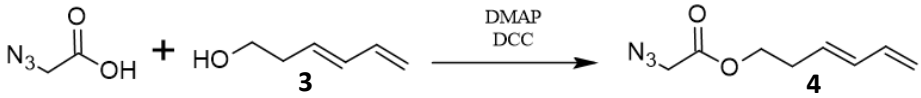
Reduction

Next, the ester **2** was reduced to the alcohol **3** using lithium aluminum hydride [16].

This reaction proceeded without hiccups and yields of 70-95% were achieved.

Esterification

To get the olefin azide product **4**, alcohol **3** was esterified with 2-azidoacetic acid via Steglich esterification [17].



Yield was 77%.

Aziridination

To achieve the key intermediate **1** from ester **4**, different conditions were utilized. The first route to be explored was aziridine formation through the triazoline intermediate.

All experiments were carried out in the following conditions:

To a vial or quartz cuvette was added 2.5 ml of solvent and 10 mg of ester **4**, followed by addition of catalyst (where applicable). The vessel was then heated or subjected to UV irradiation, as specified.

The first tries involved simple heating of the ester in different solvents and at different temperatures.

*Table 1: results of heating ester **4** in different conditions.*

Entry	Solvent	T [°C]	Time [h]	Visual result	GC
1	THF	70	3	Transparent	No change
2	$CHCl_3$	70	3	Transparent	No change
3	THF	110	24	Transparent	No change
4	$CHCl_3$	110	24	Transparent	No change
5	THF	150	24	Transparent	no change
6	$CHCl_3$	150	24	yellow	No change

7	Toluene	230 (MW)	0.5	yellow	Partial decomposition
8	Dioxane	150	3	yellow	No change
9	Dioxane	170	1.5	yellow	No change
10	Dioxane	230 (MW)	0.3	yellow	No change

After getting no positive results with THF or chloroform (entries 1-6), higher-boiling solvents were tried to be able to use higher temperatures (entries 7-10), including microwave heating (entries 7 and 10). This afforded no detectable change other than partial decomposition of the substrate in toluene (entry 7).

In an effort to make our olefin more electron-rich, Lewis acids were then utilized in addition to heating.

*Table 2 – results of heating ester **4** in the presence of Lewis acids.*

entry	Solvent	T [°C]	Catalyst	Time [h]	Visual result	GC
1	THF	50	0.5 eq AgOTf	72	Transparent	No change
2	THF	50	0.5 eq CuOTf	72	Yellow	No change
3	Dioxane	150 (MW)	0.5 eq CuOTf	0.15	Yellow, precipitate	No change
4	DMF	170 (MW)	0.05 eq CuOTf	0.15	Brown	No change
5	Dioxane	170 (MW)	0.05 eq CuOTf	0.15	Brown	No change
6	Dioxane	175 (MW)	0.5 eq AgOTf	0.15	Brown precipitate, silver coating on vial	No change
7	Dioxane	175 (MW)	0.5 eq CuOTf	0.15	Brown, precipitate	Decomposition
8	Dioxane	230 (MW)	0.5 eq CuOTf	0.3	Brown, precipitate	Decomposition

Copper triflate and silver triflate were used as Lewis acids, and temperatures were varied from 50 °C to 230 °C. Increasing temperature produced change of color, then formation of precipitate, then decomposition of substrate, but no desired reaction. The change of color and formation of precipitate, but no detectable reaction (entries 2-6), especially as evidenced by the formation of a silver coating with the use of silver triflate (entry 6), indicate decomposition of the catalyst.

Our attention was then turned to exploring the other route, aziridine formation through the nitrene intermediate.

To this end, a 400 W medium pressure mercury arc UV lamp was utilized.

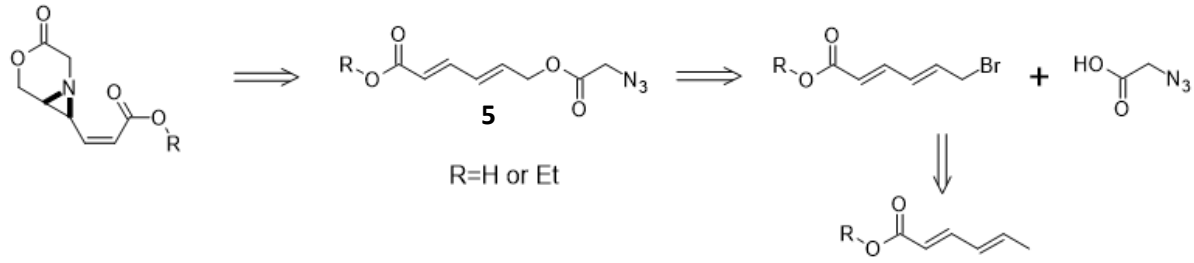
*Table 3 – results of UV irradiation on ester **4** in various conditions.*

Entry	Solvent	T [°C]	Catalyst	Time [h]	Visual change	NMR
1	DCM	rt	-	2.5	-	No change
2	Toluene	rt	-	2.5	-	No change
3	DCM	0	-	0.25	-	No change

4	DCM	0	-	1	-	No change
5	DCM	rt	-	0.25	-	No change
6	DCM	rt	-	1	-	No change
7	DCM	rt	CuOTf 0.05 eq	2.5	-	No change
8	DCM	rt	AgOTf 0.05 eq	2	Red precipitate	No change
9	heptane	rt	AgOTf 0.05 eq	16	Brown precipitate	Decomposition

First simple irradiation in solvent was used (entries 1 through 6). This yielded no change in the starting material. Addition of triflates (entries 7-9) did not improve the results, but addition of silver triflate showed a tendency to form a precipitate, probably a decomposition product of the triflate, which, in turn, reacted with the starting material (entry 9). The fact that prolonged exposure (2.5 h) to a strong (400 W) source of UV radiation produced no change in the starting material, towards the desired product or otherwise, is surprising and puzzling.

To find out if the inactiveness of the double bond moiety is the reason for the lack of results so far, model compound **5** with an activated double bond system was envisioned and retrosynthetically analyzed:



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As the first step, bromination of sorbates was tried under various conditions.

Table 4 – results of attempts at bromination in different conditions.

Entry	Substrate	Initiator	NBS	Solvent	T [°C]	Time [h]	Result
1	Sorbic acid	AIBN 10^{-5} eq	0.6 eq	$CHCl_3$	65	3.5	n.r.
2	Sorbic acid	UV 400 W	0.6 eq	$CHCl_3$	r.t.	19	Decomp.
3	Ethyl sorbate	AIBN 10^{-3} eq	0.6 eq	CCl_4	65	3.5	n.r.
4	Ethyl sorbate	AIBN 10^{-3} eq	0.6 eq	DCM	40	3	n.r.
5	Ethyl sorbate	UV 400 W	0.6 eq	DCM	r.t.	19	Decomp.
6	Ethyl sorbate	NH_4OAc 0.1 eq	1.05 eq	Et_2O	r.t.	1	Mixture of products
7	Ethyl sorbate	pTsOH	0.25 eq	DCM	40	20	n.r.

8	Sorbic acid	AIBN 0.02 eq	0.6 eq	CCl_4	65	20	~10% conversion (NMR)
9	Ethyl sorbate	BPO 0.02 eq	1.5 eq	Benzene	80	4	~20% conversion (NMR)
10	Sorbic acid	BPO 0.02 eq	1.5 eq	Benzene	80	4	Overbromination
11	Sorbic acid	BPO 0.02 eq	1.05 eq	Benzene	85	1	Mixture of products
12	Ethyl crotonate	BPO 0.02 eq	1.05 eq	CCl_4	85	3	Side reaction (NMR)

This approach ran into immediate problems. Even though the terminal radical bromination of sorbates has not been done before, analogous reactions with crotonates are reported on many occasions with excellent yields [18,19]. Utilizing similar conditions with sorbates yielded either poor conversion (entries 1-5, 7-9) or poor selectivity (entries 6, 10-11).

In light of these results, the substrate was switched to ethyl crotonate and the exact conditions used in literature were employed (entry 12) [20]. However, this approach unexpectedly led to an unidentified side reaction. This suggests that a factor not mentioned in the literature procedures but crucial to the success of the reaction is at play with all of the brominations and prevents them from giving positive results.

At this point, the time allocated for this project ran out and no more reactions could be done.

Conclusion

To conclude, it must be admitted that the project result overall was negative. No feasible route to the key intermediate **1** was completed, nor a probable route identified. Perhaps using a different UV lamp or a different Lewis acid could promote either the formation of nitrene or progress of the 1,3-dipolar cycloaddition, respectively. Otherwise, the approaches handled in this project seem to be dead ends.

Experimental

Ethyl-(3*E*)-hexa-3,5-dienoate (IVA-015)

A 50 ml Schlenk flask was flame-dried and charged with 15,25 ml of dry THF and 1,125 ml (0,8115 g, 8,0 mmol, 1,2 eq) of DIPA. The flask was cooled to -78 °C. Then 3,208 ml of 2,5 M BuLi in THF (8,0 mmol, 1,2 eq) was added dropwise over 15 minutes. The flask was left to stir for 1 hour. Then 0,816 ml (0,8653 g, 6,7 mmol, 1 eq) of DMPU was added dropwise over 10 minutes. Then the flask was left stirring for 30 minutes. Meanwhile, another flask was flame-dried and charged with 1 ml of ethyl sorbate (0,956 g, 6,7 mmol, 1 eq) and 2 ml of dry THF. This solution was added to the first flask dropwise over 20 minutes. The second flask was washed with 1 ml of THF, which was then slowly added to the first flask as well. Adding the sorbate caused the reaction mixture to turn yellow. Over 1 hour of reaction, the mixture turned orange, then deep red. A GC sample confirmed the completion of the reaction. 1,5 hours after adding the sorbate solution, the reaction mixture was quenched by adding 3 ml of EtOH over 30 minutes. After this, the reaction mixture was rapidly poured into a separation funnel containing 10 ml of water and EtOAc 3:1 mixture. The water phase was then twice extracted with 25 ml of Et_2O and the organic phase dried ($MgSO_4$), filtered and concentrated *in vacuo*. Distillation in a kugelrohr apparatus at 100 °C and 5 mbar yielded 0,6577 g (70%) of **IVA-015** as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (1H, ddd, *J* = 20.0, 10.2, 10.2 Hz, 5-***H***), 6.14 (1H, dd, *J* = 14.8, 11.0 Hz, 4-***H***), 5.78 (1H, dt, *J* = 14.8, 7.1 Hz, 3-***H***), 5.16 (1H, d, *J* = 16.9 Hz), 5.06 (1H, d, *J* = 10.2, 6-***H***), 4.14 (2H, q, *J* = 7.2 Hz, C***H***$_2$CH$_3$), 3.11 (2H, d, *J* = 7.3 Hz, 2-***H***), 1.23 (3H, t, *J* = 7.9 Hz, CH$_2$C***H***$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (***C***-1), 136.4 (***C***-5), 134.3 (***C***-4), 125.7 (***C***-3), 116.8 (***C***-6), 60.7 (***C***H$_2$CH$_3$), 38.0 (***C***-2), 14.2 (CH$_2$***C***H$_3$).

(3*E*)-hexa-3,5-dien-1-ol (IVA-019)

A 250 ml two-necked flask was flame-dried and 0,7803 g (19,5 mmol, 1,05 eq) of $LiAlH_4$ was added and the flask flushed with nitrogen. The flask was cooled to 0 °C. 60 ml of dry Et_2O was added. A solution of 2,6609 g (18,6 mmol, 1 eq) of ethyl-(3*E*)-hexa-3,5-dienoate in 10 ml of dry Et_2O was added dropwise over 15 minutes. After 50 minutes, a GC sample confirmed the completion of the reaction. The reaction was quenched with a saturated aqueous solution of Rochelle's salt dropwise over 40 minutes and left to stir over the weekend. Then the organic phase was separated from the water solution and the organic phase washed with brine and dried ($MgSO_4$). Filtration and concentration *in vacuo* yielded 1,7365 g (95%) of **IVA-019** as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (1H, ddd, *J* = 20.3, 10.1, 10.1 Hz, 5-***H***), 6.17 (1H, dd, *J* = 15.2, 10.5 Hz, 4-***H***), 5.69 (1H, dt, *J* = 14.8, 7.4 Hz, 3-***H***), 5.14 (1H, d, *J* = 17.0 Hz, 6-***H***), 5.02 (1H, d, *J* = 10.2 Hz, 6-***H***), 3.69 (2H, dt, *J* = 6.3, 5.8 Hz, 1-***H***), 2.37 (2H, dt, *J* = 6.8, 6.3 Hz, 2-***H***), 1.26 (1H, t, *J* = 7.2 Hz, O***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8 (***C***-5), 133.8 (***C***-4), 130.5 (***C***-3), 115.9 (***C***-6), 61.9 (***C***-1), 35.9 (***C***-2).

(3*E*)-hexa-3,5-dien-1-yl azidoacetate (IVA-017)

A 100 ml flask was flame-dried and charged in order with 0,2689 g (2,2 mmol, 0,5 eq) of 4-DMAP, 21 ml of dry THF, 0,404 ml (0,5449 g, 5,2 mmol, 1,2 eq) of 2-azidoacetic acid and 0,4277 g (4,4 mmol, 1 eq) of (3*E*)-hexa-3,5-dien-1-ol and cooled to 0 °C. Another flask was flame-dried and charged with 1,3624 g (6,5 mmol, 1,5 eq) of DCC and 5 ml of dry THF. The DCC solution was added into the first flask dropwise over 10 minutes. A yellow precipitate formed. After 2 hours the ice bath was removed and the reaction left overnight. The next day the reaction mixture had turned brown. TLC analysis (10% EtOAc/hex) showed that only traces of the starting material remained and the reaction had gone to near-completion. The reaction mixture was vacuum-filtered and concentrated *in vacuo* to give a dark red solid. The crude product was dry-loaded with 7 g of silica onto a column and flashed (5-10% EtOAc/hex) to afford 0,6116 g (77%) of **IVA-017** as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (1H, ddd, *J* = 20.5, 10.2, 10.2 Hz, 5-***H***), 6.14 (1H, dd, *J* = 15.2, 10.5 Hz, 4-***H***), 5.64 (1H, dt, *J* = 14.6, 7.1 Hz, 3-***H***), 5.15 (1H, d, *J* = 16.9 Hz, 6-***H***), 5.04 (1H, d, 10.2 Hz, 6-***H***), 4.25 (2H, t, *J* = 6.7 Hz, 1-***H***), 3.87 (2H, s, C***H***$_2$N$_3$), 2.46 (2H, dt, *J* = 13.6, 6.9 Hz, 2-***H***); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3 (***C***OO), 136.6 (***C***-5), 133.8 (***C***-4), 129.0 (***C***O-3), 116.4 (***C***-6), 64.8 (***C***-1), 50.2 (***C***N$_3$), 31.7 (***C***-2).

References

1 *Phytochemistry,* **2015**, *116*, 269-282.
2 *Helv. Chim. Acta,* **1948**, *31*, 1062-1066.
3 *Chem. Pharm. Bull.,* **1984**, *32*, 3789-3791.
4 *J. Org. Chem.,* **1968**, *33*, 481.
5 *Tetrahedron Lett*., **1971**, *28*, 2609.
6 *J. Chem. Soc. Perkin Trans., 1*, **1975**, 305.
7 *Tetrahedron Lett.,* **1996**, *52*, 5407.
8 *Tetrahedron Lett.,* **2001**, *42*, 9175.
9 *J. Org. Chem.,* **1988**, *53*, 2094.
10 *J. Org. Chem.,* **1989**, *54*, 3973.
11 *J. Org. Chem.,* **1990**, *55*, 4683.
12 *Eur. J. Org. Chem.,* **2007**, 6053.
13 *J. Am. Chem. Soc.,* **2011**, *133*, 19342.
14 *J. Chem. Soc., Perkin Trans. 2*, **2001**, 1781-1784.
15 *Chem. Commun.,* **2014**, *50*, 2919.
16 *J. Am. Chem. Soc.,* **2011**, *133*, 14892–14895.
17 *Angew. Chem., Int. Ed.,* **2004**, *43*, 3471-3473.
18 *Bioorganic & Medicinal Chemistry*, **2014**, *22*, 2366-2378.
19 *Archiv der Pharmazie (Weinheim, Germany)*, **2014**, 347(8), 552-558.
20 *J. Am. Chem. Soc.,* **1953**, *75*, 1895-1900.